## DETAILED ACTION

Claims 56-72, 74, 78, 80-118 are pending in the application. Claims 65-72, 74, 78, 80-92, 94-99, 101, 102, 107-109 are withdrawn from consideration. Claims 56-64, 93, 100, 103-106, 110-118 are currently under examination.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/11/2011 has been entered.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56-64, 93, 100, 103-106, 110-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reff, Cockett and Rao et al., in view of Antoniou et al (WO 00/05393, see IDS).

Reff et al. teach preventing and delaying apoptosis by expressing one or more anti-apoptotic polypeptides such as E1B-19K and Aven in the cell (see page 5, [0013]), wherein the expression of said anti-apoptotic protein results in the increased production of a cell related product, such as an antibody to anti-CD20 antibodies etc (see page 5, [0014]). Reff et al. teach that such suitable host cells for large scale production of recombinant protein may be CHO cells, BHK cells or COS cells (page 11, [0050]).

However, Reff et al. do not teach expression vector encoding the polypeptide of interest is under the control of a promoter that responds to a transactivator, and the inclusion of IRES, UCOE, and use retroviral vector.

Cockett et al. teach vectors expressing adenovirus 5 E1A or mutant are introduced into CHO-K1 cells in order to transactivate the hCMV-MIE promoter. Cockett et al. teach that hCMV-MIE promoter is highly efficient in CHO cells (see page 319, 2nd col., 2nd paragraph, line 1). Cockett et al. demonstrate that E1A protein and its mutant can activate the activity of hCMV-MIE promoter in CHO cells, and increases the production of TIMP in cell culture (see Table 1, and page 321, 1st col., 2nd paragraph). Cockett et al. further teach that high level expression of E1A, however, is toxic to cells (see page 322, 1st col., 3rd paragraph).

Rao et al. teach expression of adenovirus E1A protein renders cell susceptible to apoptosis (see page 7743, 2nd col., 2nd and 3rd paragraph). Rao et al. further teach that expression

of E1B-19K and Bcl-2 protects cell from E1A induced apoptosis (page 7743, 2nd col., 4th paragraph, and 7745, Figure 5 and legend).

Antoniou et al. teach the isolation of a polynucleotide comprising a ubiquitous chromatin opening element from hnRNP promoter, which comprises an extended methylation free CpG island. Antoniou et al. teach that such UCOE maintains stable expression of exogenous gene in recombinant cells (see page 84, lines 1-28). Antoniou et al. also teach the inclusion of IRES in vector for expressing foreign gene (see page 13, line 25), and the vectors may be integration vectors such as retroviral vectors (see page 14, lines 6-15).

It would have been obvious to an ordinary skill in the art to transfect a vector encoding a transactivator such as E1A into the recombinant host cell for producing a polypeptide of interest such as a recombinant antibody based on the combined teaching of Reff et al., Cockett et al. and Rao et al. The ordinary skill in the art would realize the advantage of using such transactivator because Cockett et al. have demonstrated that said protein can transactivate the activity of hCMV-MIE, a promoter commonly used in CHO cells for producing recombinant protein. The ordinary skill in the art would recognize that use of such transactivator at high level may induce apoptosis of the host cell, which is not desirable for producing recombinant protein, and therefore, transfecting a apoptosis protecting protein to overcome such toxicity based on the teaching of Rao et al. Since Rao et al. already demonstrated the feasibility of inhibiting apoptosis by expressing E1B-19K and Bcl-2 in BHK cells, and Reff also demonstrate that expressing E1B-19K and Aven can protect cells from apoptosis in CHO cells, absent evidence from the contrary, the ordinary skill in the art would have reasonable expectation of success to develop a system comprising vectors that express E1A, Bcl-2 and/or E1B, and transfecting them

to recombinant protein producing host cells such as BHK or CHO to increase the production of recombinant protein. It would also have been obvious to an ordinary skill in the art to include cis element such as the hnRNP UCOE and IRES to the vector system discussed by Reff, Rao and Cockett for producing recombinant protein, as well as use retroviral vectors in such vector system. The ordinary artisan would have recognize that use of such elements would maintain stable expression of the foreign gene in a host cell (UCOE), and increase the expression of the second gene in the same vector (IRES) based on the teaching of Antoniou et al. Retroviral vectors are widely used for expressing foreign gene at the time of filing. Newly added claims 110-117 recite two fold increase and 5 fold increase in the production rate for the polypeptide of interest by combination of the transactivator and the apoptotic-protective protein. Since it is obvious to make such combination as demonstrated by Reff, Cockett and Rao, it is inherent that the production would be increased to the level as claimed. Combining prior art known elements to improve a known system based on their intended function would have been obvious to an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

***Response to Arguments***

In response to the above rejection, Applicants assert that the pending claims are not obvious because Reff publication teaches enhanced host performance when host cell life is extended beyond limiting factors that contribute to apoptosis through the use of apoptosis protective agent, wherein expressing a transactivator that would induce apoptosis would not be desirable. Applicants also assert that Reff provides no insights as to whether the claimed combination of toxic transactivator and rescuing apoptosis protective protein would enhance

recombination protein production as recited in claims 110-118. Applicants further argue that the claimed method of using toxic levels of a transactivator expressed from a strong promoter combined with rescue through an apoptosis protective protein is a different way of enhancing recombinant protein production compared to Reff, whose teaching relies on increasing the rate of production through longer host cell lifetime and greater cell density. Applicants also argue that Cocket teach high levels of transactivator inhibited the growth of host cells and high level of transactivator is undesirable for recombinant protein expression, and the teaching of Cocket suggests using a weak promoter and low level expression of E1A is desirable to enhance protein production, which is inconsistent with the recitation of using a strong promoter as claimed. Applicants assert that the combined teaching of Reff and Cocket suggests factors causing cell toxicity are to be avoided and this teaches away from the pending claims which intentially introduce into the recombinant production system a factor causing toxicity. Applicants further assert that since neither Reff nor Cockett tech toxic levels of transactivator expressed from a strong promoter for recombinant protein expression, or rescue with an apoptosis protective protein, the combination fails to teach the limitation of claims 110-118. Applicants further argue Rao is not directed to recombinant protein expression and person of skill in the art would not combine Rao with Reff and Cockett. Applicants also assert that Rao does not teach the limitations of the claim which are missing from Reff and Cockett as discussed above, and thus the combination of the three references does not teach all limitations of the pending claims. Applicants also assert that there is no reasonable expectation of success for the claimed invention based on Reff, Cockett and Rao. Morevoer, Applicants argue that Antoniou's teaching does not bridge the gaps in Reff, Cockett and Rao, regarding the expression of toxic levels of

transactivator for inducing recombinant expression with rescue by an apoptosis-protective protein, and thus fail to teach the combination will enhance protein production by 2-5 fold. Applicants further cited *Eisa*i and *kinetic Concepts* to demonstrated the combined teaching from prior art cannot drop features that are found as advantageous to make the claimed invention. Applicants argue that Reff and Cockett together extol the benefits of reducing toxicity to host cells, including apoptosis, during recombinant production of desired proteins. Applicants argue that adding toxic levels of transactivator to Reff and Cockett would be contrary to the teachings of Reff and Cockett and would require that a person of skill in the art forego the advantages feature taught by these references, because the object of Reff is to reduce natural apoptosis and it would be antithetical to that goal to artificially introduce to the host cell factors that would increase apoptosis over the natural factors, while Cockett bolsters this by teaching toxic levels of transactivator are undesirable for recombinant protein expression. Applicants further cited Federal Circuit decision *Kinetic Concepts, Inc, v. Blue Sky Med. Grp, Inc.,* to address the combined teaching of Reff, Cockett, Rao and Antoniou do not teach the limitation of "expressing the transactivator at a level that could cause death of the host cell in the absence of the apoptosis protective protein, and wherein the apoptosis protective protein prevents cell death from the transactivator" and this combination will increase protein production by 2-5 fold, just as they do not address "treating a wound with negative pressure" in this case. Applicants thus conclude that the claimed invention is not obvious in view of the combined teaching of Reff, Cockett, Rao and Antoniou.

The above argument has been fully considered but deemed unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants are reminded that the rejection is not based on Reff, Cockett, Rao and Antoniou individually, but rather the combination of the teaching as a whole. Further, the Applicant's characterization of the teaching of Reff, Cockett, Rao and Antoniou is off the mark because Applicants does not view the entire teaching of references as a whole. In the instant case, Reff has demonstrated that increased production of a polypeptide of interest as a result of expressing the anti-apoptotic protein, while the teaching of Cockett has indicated that it is desirable to express E1A that improves recombinant protein production through transactivation, although cell growth inhibition is an issue at high level of E1A expression. The teaching of Rao provides evidence that E1A renders cell susceptible to apoptosis but expression of E1B-19K and Bcl-2 protects cell from E1A induced apoptosis. Although the teaching of Rao is not directed to recombinant protein production, it would have been obvious to an ordinary skill in the art that high level E1A expression in recombinant protein production would likely have the same problem because the effect of high level of E1A that inhibits cell growth has been demonstrated by Cockett. As such, the ordinary skill in the art would recognize that this potential problem illustrated by Cockett may be overcome by expression anti-apoptotic gens such as E1B-19K and Bcl-2. There is reasonable expectation of success to use such combination of vectors because all the vectors and sequences encoding such factors have been known in the prior art as evidenced by the teaching of Reff, Cockett, Rao and Antoniou, and transfecting said vectors to a host cell such as CHO would have been within the capability of an ordinary artisan. With regard to the limitation of increasing the production of 2-5 fold, since it would have been

obvious to make such combination as demonstrated by Reff, Cockett and Rao, it is inherent that the production would be increased to the level as claimed. Moreover, contrary to Applicants' assertion, Cockett teaches using a strong promoter, hCMV-MIE for direct expression of E1A (see p321, Figure 1A and legend). The instant case is completely different from cited *Eisai* and *kinetic Concepts* because there is no alleged advantageous being dropped in the analysis for whether the invention would have been obvious. Moreover, the decision of *Kinetic Concepts, Inc, v. Blue Sky Med. Grp, Inc.* does not apply to the instant case because the factual basis is different between the decision and current application. The Federal decision reached the conclusion of non-obviousness based on the construction of the term "wound" which is defined by that specification being exclusively skin wound, not other types of injury taught by the prior art. In the instant case, the teaching of the specification does not render the combined teaching of prior art non-obvious because the specification does not provide a limiting definition for such toxic level of expression or set forth a range for the expression level. Therefore, the claimed invention is obvious in view of the teaching of the cited art for reason given above.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 110-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 110-118 recite the limitation of production rate of the antibody being enhanced at least two fold or fivefold by the combination of the transactivator and the apoptosis protective protein. This newly added limitation is not supported by the specification as originally filed because the specification does not describe the combination of expressing the transactivator and the apoptosis protective protein would enhance the production rate of an antibody to at least two fold or five fold. Therefore, this newly added limitation constitutes new matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 9:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636